PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100852-1WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/001124	International filing date *(day/month/year)* 16.03.2004	Priority date *(day/month/year)* 19.03.2003
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant ASTRAZENECA AB et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.09.2004	30.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Telephone No. +31 70 340- van Klompenburg, W.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/001124

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-51 as originally filed

Sequence listings part of the description, Pages

1-31 as originally filed

Claims, Numbers

1-27 as originally filed

Drawings, Sheets

1-8 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-20,24,25 (completely)

because:

☒ the said international application, or the said claims Nos. 18 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 18-20 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 18-20 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 18,20,24,25 (completely)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-23,26,27 (all completely), .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,8,9,14-17,23,26,27
	No:	Claims	1-3,5-7,12,13,21,22
Inventive step (IS)	Yes:	Claims	4,8,9,15-17,23,26,27
	No:	Claims	14
Industrial applicability (IA)	Yes:	Claims	1-17,19,21-23,26,27
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No search report has been established for claims 24,25 due to a lack of unity (see Item IV).
Claim 18 is not searched since it was a method of treatment and no search could be performed for the alleged effect of the compound, since such a compound was not defined in technical terms.
Claims 19,20 were excluded from search. The claims attempt to define the subject-matter in terms of a result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.
Claims 16,17 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of a result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. It is noted that apart from the RORalpha-UNC5C fusion no further obesity susceptibility gene is identified in the present application. The search of claims 16,17 has only been carried out for said fusion gene/polypeptide.

The applicant is reminded that claims or parts thereof for which no International Search Report has been established, will not be the subject of the International Preliminary Examination (Rules 66 (1) (e); 70 (2) (d) PCT).

Re Item IV

Lack of unity of invention

This Authority considers that there are 3 inventions covered by the claims indicated as follows:

Invention 1, claims 8,9,14-23,26,27 (completely), claims 1-4,6,7,12,13 (partially)

An isolated nucleic acid molecule, comprising a sequence having at least 65% identity to a variant of SEQ ID NOs:1,3. A vector, a host cell. A purified RORalpha1-UNC5C fusion polypeptide. A method for detecting a polynucleotide, a method for detecting an obesity susceptibility gene, a method for detecting a translocation junction, a method for

identifying a compound. A method of treating a subject, use of a compound, a pharmaceutical composition, a method of making a pharmaceutical composition, a method determining altered level of expression. A method of diagnosing obesity, comprising analysing presence of RORalpha1-UNC5C mRNA or fusion polypeptide.

Invention 2, claims 5,10,11 (completely), claims 1-4,6,7,12,13 (partially)

An isolated nucleic molecule comprising a sequence having at least 65% identity to a degenerate variant of SEQ ID NO: 7. A vector, a host cell. A purified RORalpha 5 polypeptide, a method for producing a protein, a method for detecting a polynucleotide.

Invention 3, claims 24,25 (completely)

A method of diagnosing obesity, comprising determining the level of UNC5C mRNA or protein

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

Genes and chromosomal locations involved in the development of obesity are known in the prior art, see for example Chagnon et al. 2004 Obesity Reasearch, pp313-367 (D1). RORalpha variants are also known from the prior art, see for example Jetten et al. (2001) Progress in Nucleic Acid Research and Molecular Biology, Vol.69, pp. 205-247 (D2). D1 discloses (Tables 1,3,5) several genes, proteins and chromosomal locations involved in obesity, notably the 15q22 region is mentioned to be involved in obesity related disorders (Table 3). D2 describes the ROR families and subfamilies, pages 208 and 209 describe the existence of four isotypes of ROR alpha. In the light of the prior art documents D1, D2, the problem underlying the application can be defined as the provision of further genes and proteins as markers for obesity. The solutions as described and claimed are: The RORalpha1-UNC5C fusion polypeptide/gene, the RORalpha5 polypeptide gene and the UNC5C protein. In view of the fact that genes and proteins related to obesity and their chromosomal locations have already been disclosed in the prior art, due to the essential differences in structure and putative

functions of the polynucleotides and polypeptides and due to the fact that no other technical features can be distinguished which, in the light of the prior art, could be regarded as special technical features common to these solutions, the ISA is of the opinion that there is no single inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT. Consequently there is a lack of unity.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/29058 A (ALSOBROOK JOHN P II ; BURGESS CATHERINE E (US); MALYANKAR URIEL M (US)) 11 April 2002 (2002-04-11)

D2: CHAGNON Y C ET AL: "THE HUMAN OBESITY GENE MAP: THE 2002 UPDATE" OBESITY RESEARCH, BATON ROUGE, LA,, US, vol. 11, no. 3, 14 March 2003 (2003-03-14), pages 313-367, XP008026392 ISSN: 1071-7323

D3: BRUFORD E A ET AL: "Linkage Mapping in 29 Bardet-Biedl Syndrome Families Confirms Loci in Chromosomal Regions 11q13, 15q22.3-q23, and 16q21" GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 41, no. 1, 1 April 1997 (1997-04-01), pages 93-99, XP004459343 ISSN: 0888-7543

D4: US 2002/169287 A1 (MCMILLAN JANINE SUSAN ET AL) 14 November 2002 (2002-11-14)

D5: WO 01/78894 A (GENOME THERAPEUTICS CORP) 25 October 2001 (2001-10-25)

D6: SUNDVOLD H ET AL: "Identification of a novel peroxisome proliferator-activated receptor (PPAR) gamma promoter in man and transactivation by the nuclear receptor RORalpha1." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. 21 SEP 2001, vol. 287, no. 2, 21 September 2001 (2001-09-21), pages 383-390, XP002309631 ISSN: 0006-291X

D7: WO 99/50660 A (RASPE ERIC ; BONHOMME YVES (FR); MERCK PATENT GMBH (US)) 7 October 1999 (1999-10-07)

D8: WO 02/094990 A (BANDMAN OLGA; INCYTE GENOMICS INC ; KALLICK DEBORAH A (US); XU YUMING) 28 November 2002 (2002-11-28)

D9: WO 93/06215 A (SALK INST FOR BIOLOGICAL STUDI) 1 April 1993 (1993-04-01)

D10: GIGUERE V ET AL: "The orphan nuclear receptor ROR-alpha (RORA) maps to a conserved region of homology on human chromosome 15q21-q22 and mouse chromosome 9" GENOMICS, vol. 28, no. 3, 1995, pages 596-598, XP002309632 ISSN: 0888-7543

0 Invention 1,

Items 1 and 2 below relate to invention 1, the fusion product between ROR alpha and UNC5C as well as the general claims 21 and 22

1 Novelty (Art. 33(2) PCT)

1.1 D1 discloses (SEQ ID NO: 125) an UNC5C-like protein with 97% identity in 913 amino acids overlap. D1 further discloses vectors, host cells, methods of detection etc. (claims 1-36). In the light of D1, the very broad formulated claims 1-3, 6, 7, 12 lack novelty.

1.2 Claims 21-22 refer to methods of making pharmaceutical compositions against all possible obesity susceptibility genes without limitation to a gene or chromosomal location. D4 (claim 41) and D5 (claims 53-61,63-72) disclose methods of making pharmaceutical compositions identical to the methods of claims 21 and 22. Claims 21 and 22 therefore lack novelty (Art. 33(2) PCT).

2 Inventive Step (Art.33(3) PCT)

Claim 14 concerns a method to identify an obesity susceptibility gene located near 4q22.3 and/or 15q22.2. The difference with the prior art is that the influence of this particular chromosomal translocation on the expression of genes in the mentioned areas is checked. It is not clear that there is any technical effect or advantage of using this genetic model over using any other model which has already pointed to the same chromosomal region. D2 discloses in tables 1,3,5 lists of genes and chromosomal locations known to be involved in obesity, including the areas near 4q22 and 15q22

(table 5). Finding candidate obesity susceptibility genes by screening for aberrant expression of genes in these locations in affected subjects is obvious to a person skilled in the art. Additionally D3 discloses the involvement of 15q22.3 in Bardet-Biedl Syndrome which also includes obesity. Therefore it is concluded that the subject matter of claim 14 does not involve an inventive step (Art. 33(3) PCT.

3 Invention 2

The items below relate to invention 2, ROR-alpha (SEQ ID Nos: 7,8)

4 Novelty (Art. 33(2) PCT)

4.1 D8 discloses SEQ ID NO:51, which has 100% identity with SEQ ID NO:7 of the present application in 837 nucleotide overlap. The corresponding amino acid sequence, SEQ ID NO:25 is identical to SEQ ID NO:8 over a stretch of 336 amino acids. The claims of D8 further anticipate vectors, host cells purified polypeptide, a method of producing a polypeptide and a method of detecting polynucleotide. Therefore it is concluded that claims 1-3,5-7,10,11-13 are not novel (Art. 33(2) PCT)

4.2 D9 concerns members of the thyroid/steroid receptor family. SEQ ID NO:1 of D9 is 99.8 % identical over a stretch of 1570 nucleotides to SEQ ID NO:7 of the present application. The claims and example 1 of D9 further describes vectors, host cells, purified polypeptide and methods for producing polypeptides. Therefore D9 renders claims 1-3,5-7,10,11-13 not novel (Art. 33(2) PCT).

5 Inventive Step (Art.33(3) PCT)

Claim 16 relates to a method of identifying a test compound that modulates the **expression** of an obesity susceptibility gene at chromosome cytoband 4q22.3 or 15q22.2. Claim 17 relates to compound which modulate the **activity** of such a gene. As described in D4 and D5 (see point 1 above) methods for identifying test compounds that modulate expression or activity of an obesity susceptibility gene were known. Therefore the difference is that the susceptibility gene in the present application is ROR-alpha. There seems to be no technical effect related to this difference. The problem is therefore regarded to be the provision of further obesity susceptibility genes. The solution is than: providing ROR-alpha. This solution is known from the prior art. D9 describes the involvement of ROR alpha in obesity. Figures 2 and 3 show functional binding of ROR-ALPHA to the promoter region of PPAR-gamma. PPAR-gamma is well known to be involved in obesity (p383, last line of the lefthand column -top of the right-hand column). Therefore it is concluded that the person skilled in the art, looking for further genes involved in obesity would use ROR-ALPHA in any of the generic assays

screening for modulators as mentioned in D4 and D5, without applying inventive skills. Therefore it is concluded that the subject-matter of claims 16,17 is not inventive (Art. 33(3) PCT).